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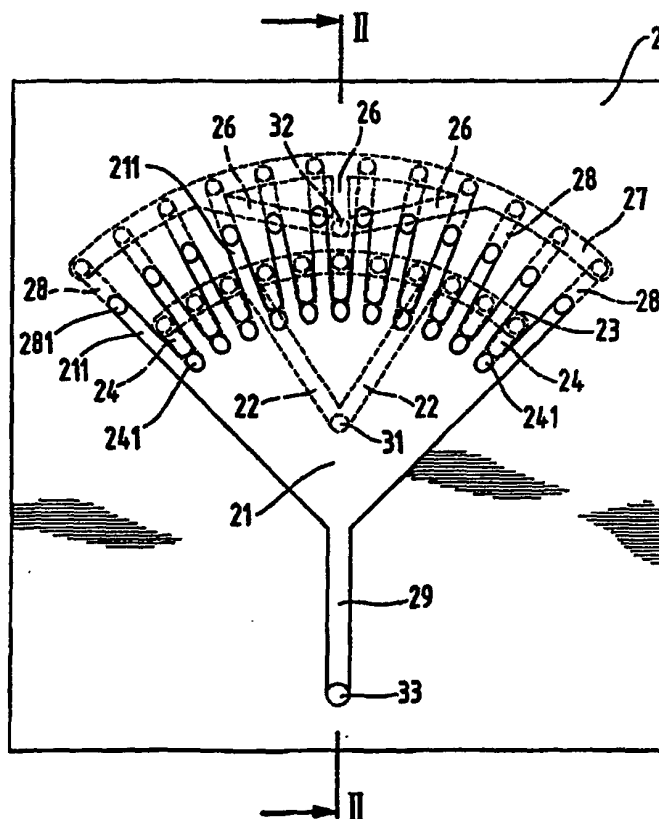
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(54) Title: FLOW CELL FOR THE PASSIVE MIXING OF FLOWABLE SUBSTANCES

(57) Abstract

A flow cell for the passive mixing of at least two flowable substances has an inlet opening (31, 32) for each substance, a common outlet opening (33) and a planar flow bed (21) for mixing the substances. There is provided for each substance a distributor that is arranged between the inlet opening (31, 32) for the substance in question and the flow bed (21) and that divides the substance into a plurality of physically separate thin streams. The distributors supply the thin streams to the flow bed (21) in such a manner that, in the flow bed, adjacent thin streams in contact with one another contain different substances.



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Flow cell for the passive mixing of flowable substances

The invention relates to a flow cell for the passive mixing of flowable substances according to the preamble of the independent patent claim.

Apparatuses for mixing flowable substances are used, for example, in many areas of analytical chemistry and of medical diagnostics, in chemical reactions, for example for investigating the kinetics of rapid reactions, in process measurement technology and in environmental analysis. They can be divided into apparatuses in which passive mixing of the substances takes place and those in which the substances are mixed actively. In that context, the term "passive" means that the mixing takes place during laminar flow of the substances. That type of mixing is typically diffusion-controlled; in particular, apparatuses for passive mixing are free of moving stirring or mixing elements. In contrast, the term "active" denotes mixing with turbulent flow. Those turbulences can be produced in a mixing apparatus, for example using moving stirring elements, for example mechanically driven stirrers or magnetic stirrers. Another possible means of mixing substances actively, without using moving stirring elements, is to increase the Reynolds number to beyond the critical limit of approximately 2100 in order to produce the transition from laminar flow to turbulent flow. That can be achieved, for example, by means of special geometries for the flow channels, or the mixing chambers, in which the substances move, and by very high flow rates for the substances. It is also known from the prior art to provide in the flow path of the substances, for better active mixing, baffles that deflect the streams of fluid and contribute to the creation of turbulence.

Efforts are being made these days increasingly to miniaturise analytical systems and to put together such systems in modular form from individual components. In that case also there is frequently a need to mix different substances together as rapidly and as homogeneously as possible. However, known apparatuses for active mixing are not very suitable in practice for such miniaturised analysis systems ("miniaturised total chemical analysis systems", μ -TAS) because they often have large internal volumes. In addition, the integration of moving stirring elements and/or their drive elements into such miniaturised systems is scarcely possible, since the amount of space required and the cost of the construction of such mixing apparatuses are comparatively large. In

addition, the moving components are subject to wear, with the result that, in general, their functioning is guaranteed for a limited time only.

In other known mixers that are free of moving stirring elements, high flow rates have to be generated in order for the substances to be mixed rapidly by turbulent flow. In flow channels of small to very small dimensions, such as capillaries, turbulent flow is, however, either very difficult to achieve or can be achieved only locally, for example at the edges, and at very high flow rates. Especially in the case of highly viscous substances, such as blood or fermentation culture media, it is even more difficult to reach a Reynolds number sufficiently high for turbulent flow.

Although apparatuses for the passive mixing of substances that are known from the prior art do not have some of the drawbacks and limitations mentioned, they do have the disadvantage that passive mixing takes significantly longer than does active mixing. Since mixing under laminar flow conditions takes place as a result of the diffusion of particles from the fluid stream of one substance into that of another substance, the different substances have to be in contact long enough for complete mixing to be achieved. However, that leads to a considerable increase in the time required for a measurement or for an analysis. That problem is especially pronounced, for example, in the case of high-molecular species and when the concentrations of the substances to be mixed in the fluid streams are low. An attempt is sometimes made to reduce those difficulties by means of a temperature increase, but that procedure poses fresh problems, because, for example, biological species are frequently heat-labile. It is also known from the prior art to accelerate the passive mixing of substances by dividing the fluid streams to be mixed into part streams, rotating those part streams relative to one another in space and then bringing them back together again. That measure brings about an increase in the effective contact surface between the different substances and reduces the length of the diffusion paths to be travelled. Mixing apparatuses that operate in accordance with that method are known, for example, as "static mixers" and are available, for example, from GLT mbh Pforzheim (Germany). Those mixers consist of a series of stationary, specially shaped deflecting elements which are arranged in a flow pipe, in the form of a helical unit. Streams of fluid passed through such a mixer are progressively separated, rotated relative to one

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another in space and brought back together again. However, such static mixers have a large volume, and the diameter of the flow pipes is typically at least several millimeters. Owing to the complex structure of the deflecting elements, such mixers are not very suitable, from the constructional point of view, for miniaturisation or for use in miniaturisable systems.

On the basis of that prior art, it is therefore an aim of the invention to provide an apparatus for the passive mixing of flowable substances that allows significantly more rapid mixing under laminar flow conditions. The apparatus should be easy to miniaturise and should have as little dead volume as possible so that it can be used even for small to very small volumes of substance. Furthermore, the apparatus should be capable of integration without great effort into relatively complex systems of modular, especially stack-like, construction. In particular, the apparatus should be suitable for miniaturised analysis systems (μ -TAS). The apparatus should also be easy to manufacture and suitable for economic mass production.

The apparatus that achieves those aims is the flow cell for the passive mixing of at least two flowable substances that is characterised by the features of the independent patent claim. Since the distributors divide each substance into a plurality of physically separate thin streams and supply those thin streams to the substantially planar flow bed in interspersed relationship so that, in the flow bed, adjacent thin streams that are in contact with one another contain different substances, the thin streams lying next to one another in one plane, there is a marked increase in the effective contact surface between the substances to be mixed and a reduction in the length of the diffusion path from one substance to another. As a result, the substances are mixed rapidly and efficiently under laminar flow conditions. The planar arrangement of the thin streams in the flow bed brings with it a considerable simplification of the structure since the flow bed is free of structural deflecting elements for rotating the individual thin streams relative to one another in space. The flow cell according to the invention can therefore also be miniaturised without difficulty. With its overall plate-like structure and substantially planar flow channel, the flow cell according to the invention is specially suitable for integration into relatively complex systems of modular, especially stack-like, construction. In particular, the flow cell can be produced on an individual planar

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module, for example in the very compact form of a chip, and can thus be used as an efficient, rapid mixing apparatus in miniaturised analysis systems, such as μ -TAS. The flexibility of the flow cell according to the invention in terms of its geometric form ensures a high degree of compatibility with numerous other components of complex flow systems.

For example, each distributor may comprise at least one supply channel, one distribution trough and at least two distribution channels. The supply channel leads from the associated inlet opening for the substance to the associated distribution trough. Each distribution channel opens at one end into the distribution trough and at the other end into the flow bed. The substances pass from the appropriate inlet opening through the supply channel or channels and into the corresponding distribution trough and flow from that trough through the distribution channels, in the form of thin streams, into the flow bed. The outlets of all the distribution channels into the flow bed, which channels of course belong to different distributors, are interspersed in such a manner that, in the flow bed, adjacent thin streams that are in contact with one another contain different substances. It is especially advantageous if the flow bed narrows as the distance from the outlets of the distribution channels into the flow bed increases, until it enters a flow channel leading to the outlet opening. As a result of that measure, the thin streams are 'focused', in the direction of flow, onto the flow channel which may have, for example, capillary dimensions, i.e. they are brought increasingly closer together. As a result, the diffusion paths between the individual thin streams are reduced in length, leading to further acceleration of the mixing operation.

The flow cell according to the invention can be constructed, for example, in such a manner that it comprises, in a stack-like arrangement, a base plate, a main body and a cover plate, the main body being arranged between the base plate and the cover plate. The main body has on its boundary surface facing the cover plate a cut-out portion that forms the flow bed. On its boundary surface facing the base plate the main body has further cut-out portions that form the supply channels and the distribution troughs. The inlet openings and the outlet opening are provided in the base plate, which can be connected to the main body in such a manner that it covers the supply channels and the distribution troughs. The cover plate can be connected to the main body in such a

manner that it covers the flow bed. That type of structure is advantageous from a constructional point of view since, for example, it is markedly easier to produce the flow bed in the form of a cut-out portion in a boundary surface of the main body than to produce it in the interior of a solid body. In addition, that structure offers the advantage that the base plate and/or the cover plate can serve simultaneously as connecting elements to other components of relatively complex flow systems and can be adapted to such components without structural changes to the main body being required. That possibility increases the compatibility or flexibility of the flow cell according to the invention as regards its integration into such relatively complex systems.

The flow cell according to the invention can be produced, for example, from metallic materials or from plastics using processing techniques known *per se*. Suitable processes are, for example, cutting processes, especially precision engineering, micro machining processes, such as those used in microelectronics for structuring semiconductor materials, and the lithographic-galvanic LIGA process. The flow cell according to the invention can thus be made from materials known *per se* using processing techniques known *per se*. It is advantageous that a very large number of materials are suitable for the production of the flow cell since it can therefore be adapted without difficulty to the special requirements of a large number of applications.

In the flow cell according to the invention, each of the distribution troughs is preferably in the form of an arcuate trough, for example in the form of a quarter-circle. In that case, the distribution troughs belonging to different distributors run concentrically. The outlets of the distribution channels belonging to a distributor into the flow bed lie on a feed line which is also in the shape of the arc of a circle. The various feed lines also run concentrically, with the result that they have a common geometric centre which lies in the region in which the flow bed enters the flow channel. The flow bed is substantially in the form of a planar funnel. It widens from the point at which it enters the flow channel initially in the form of the sector of a circle the centre of which coincides substantially with the common geometric centre of the feed lines. The periphery of that sector of a circle includes the feed line having the smallest radius. From that feed line, the flow bed extends, in the form of radial channels that are arranged between the

outlets lying on that feed line, as far as the further outwardly lying outlets of the distribution channels.

Alternatively, in analogous manner, the distribution troughs can also be in the form of circular, concentric troughs and the feed lines can be circular. The flow bed is then in the shape of a circle with radial channels joining it at its periphery. The centre of that circle coincides substantially with the common geometric centre of the feed lines, and its periphery lies on the feed line having the smallest radius. From there the radial channels, which are arranged between the outlets lying on that feed line, extend as far as the further outwardly lying outlets.

That arcuate or circular form of the distribution troughs and feed lines has the advantage that the geometric path lengths of the individual thin streams in the flow cell according to the invention are substantially equal. As a result, the contribution of the flow cell to the axial dispersion of a substance zone is very small. "Axial dispersion" is to be understood to mean the widening of a substance zone in the direction of flow.

A variant of the flow cell according to the invention that is likewise preferred is as follows: in each distributor, the number of supply channels leading from the inlet opening to the distribution trough is equal to the number of distribution channels leading from the distribution trough to the flow bed. That measure has the advantage that it ensures that the substance is uniformly divided amongst the individual distribution channels. In each distributor there are typically up to one hundred, and especially fewer than thirty, distribution channels, generally having a diameter in the range of from 10 μm to 1000 μm . With a view to miniaturisation, however, smaller dimensions of less than 600 μm are especially preferred. Typically, the flow bed and the flow channel each have a depth of from 10 μm to 1000 μm ; in this case also, for reasons of miniaturisation, smaller dimensions of less than 200 μm are especially preferred. The flow channel preferably has a width of from 10 μm to 1000 μm , specially of less than 600 μm .

The division of each of the substances to be mixed into a plurality of thin streams that are arranged in the planar flow bed in the form of a thin stream pattern in which

adjacent thin streams contain different substances, brings about rapid and complete passive mixing of the substances. As a result, substantially shorter response times are also obtained, for example, in the case of chemical reactions or in biological assays. That has the advantage that the flow cell according to the invention can be operated even at relatively low temperatures. The simple construction of the flow cell, especially with the absence of moving mixing elements, allows the cell also to be miniaturised without difficulty, with the result that even small to very small quantities of substance can be used. That is especially advantageous in cases where the substances are available in small amounts only or are very costly.

Further advantageous measures and preferred forms of the flow cell according to the invention are to be found in the dependent claims.

The invention is explained in more detail below with reference to embodiments and to the drawings. In the diagrammatic drawings, which are not to scale:

- Fig. 1 is a plan view of the main body of a first embodiment of the flow cell according to the invention from the cover plate (without the cover plate),
- Fig. 2 is a section through the first embodiment of the flow cell according to the invention along the line II-II in Fig. 1 (with the cover plate),
- Fig. 3 is a plan view of the main body of a variant of the first embodiment of the flow cell according to the invention from the base plate (without the base plate) and
- Fig. 4 is a plan view of the main body of a second embodiment of the flow cell according to the invention from the cover plate (without the cover plate).

The following description of the invention relates by way of example to embodiments of the flow cell that are designed for the passive mixing of two flowable substances. The invention is not, however, limited to such flow cells, but relates also to flow cells that are suitable for the passive mixing of more than two flowable substances, that is to say

the description applies mutatis mutandis to embodiments for the passive mixing of more than two substances.

The flow cell according to the invention typically contains an inlet opening 31, 32 (Fig. 1) for each substance, a common outlet opening 33 for the substances and a flow bed 21 for mixing the substances. According to the invention, the flow cell has a substantially plate-like structure, the flow bed 21 being substantially planar. In addition, there is provided according to the invention a distributor for each substance, which is located between the inlet opening 31, 32 for the substance in question and the flow bed 21. The distributor first divides the individual substance into a plurality of physically separate thin streams. The various distributors then guide the thin streams to the flow bed 21 in interspersed relationship so that in the flow bed 21 adjacent thin streams that are in contact with one another contain different substances. The description of the flow bed 21 as "substantially planar" should be understood to mean that the various thin streams in the flow bed 21 lie next to one another in one plane and that the thin streams are not rotated relative to one another in space or deflected or turned out of the plane. The plate-like structure of the flow cell is preferably such that the flow cell comprises, in a stack-like arrangement, a base plate 3, a main body 2 and a cover plate 4, the main body 2 being arranged between the base plate 3 and the cover plate 4.

A first embodiment of the flow cell according to the invention, which is constructed in that stack-like arrangement, is shown in Fig. 1 and Fig. 2. Fig. 1 is a plan view of the main body 2 of the first embodiment. The plan view is from the cover plate 4 which is not itself illustrated in Fig. 1. Fig. 2 shows a section through the first embodiment, including the cover plate 4. The line II-II on which the section is based can be seen in Fig. 1. The flow cell as a whole has the reference numeral 1. The first embodiment is used for mixing two flowable substances which will be referred to hereinafter as the first substance and the second substance. The inlet opening 31 for the first substance, the inlet opening 32 for the second substance and the outlet opening 33 are in the form of drilled holes in the base plate 3. In this first embodiment, the distributor for the first substance comprises two supply channels 22, a distribution trough 23 and a plurality of distribution channels 24. The distributor for the second substance comprises three

supply channels 26, a distribution trough 27 and a plurality of distribution channels 28. Each of the supply channels 22 for the first substance extends from the inlet opening 31 for the first substance to the distribution trough 23 for the first substance. Each of the supply channels 26 for the second substance extends from the inlet opening 32 for the second substance to the distribution trough 27 for the second substance. Each of the distribution channels 24 for the first substance opens at one end into the distribution trough 23 for the first substance. At their other ends the distribution channels 24 open into the flow channel 21. The outlets of the distribution channels 24 into the flow channel are given the reference numeral 241 in Fig. 1 and Fig. 2. In analogous manner, the distribution channels 28 for the second substance open at one end into the distribution trough 27 for the second substance and at the other end into the flow channel 21. The outlets of the distribution channels 28 for the second substance into the flow channel 21 are given the reference numeral 281 in Fig. 1 and Fig. 2. In the first embodiment, the flow bed 21 is substantially in the form of a planar funnel. A more precise description of the geometry is given hereinafter. The outlets of the distribution channels 241, 281 are in the region of the broad end of the funnel. From there the flow bed narrows as the distance from the outlets 241, 281 increases in the direction of flow until it enters a flow channel 29 leading to the outlet opening 33.

In the first embodiment (see Fig. 1 and Fig. 2), the main body 2 has on its boundary surface facing the cover plate 4 a cut-out portion that forms the flow bed 21 and the flow channel 29. The cover plate 4 can be connected to the main body 2 in such a manner that it covers the flow bed 21 and the flow channel 29. On its boundary surface facing the base plate 3 the main body 2 has further cut-out portions that form the supply channels 22 and 26 and the distribution troughs 23 and 27. The base plate 3 can be connected to the main body 2 in such a manner that it covers the supply channels 22 and 26 and the distribution troughs 23 and 27. The distribution channels 24 and 28 are in the form of drilled holes that extend from the associated distribution trough 23 or 27, respectively, through the main body 2 and as far as the respective outlets 241 and 281 into the flow channel. The outlets 241 belonging to the first distributor lie on a first feed line and the outlets 281 belonging to the second distributor lie on a second feed line. The feed lines are imaginary lines each joining the outlets belonging to a distributor. In the first embodiment the two feed lines are each in the

shape of the arc of a circle, for example a quarter-circle. In addition, the two feed lines run concentrically and therefore have a common geometric centre which lies in the region in which the flow bed 21 enters the flow channel 29. The radii leading to the two ends of the second feed line - which lies further towards the outside in Fig. 2 - also include the first feed line. The distance between two adjacent outlets 241 or 281 lying on the same feed line is in each case at least as great as the diameter of an outlet. The flow bed 21, which is substantially in the form of a planar funnel, widens from the point at which it enters the flow channel 29 initially in the form of the sector of a circle the centre of which coincides with the common geometric centre of the feed lines. The periphery of that sector of a circle includes the first feed line, which has the smallest radius. From that first feed line the flow bed 21 extends in the form of radial channels 211, which begin between and adjacent to the outlets 241 lying on the first feed line, as far as the outlets 281 which lie further to the outside in Fig. 2, on the second feed line. For that purpose it is necessary for the outlets 281 on the second feed line to be arranged offset by at least the diameter of one outlet relative to the outlets 241 on the first feed line.

In the first embodiment of the flow cell 1 according to the invention, the two distribution troughs 23 and 27 are each in the form of an arcuate trough, for example in the form of a quarter-circle. In addition, the two distribution channels 23 and 27 are arranged concentrically. In addition, the vertical projection of the first distribution trough 23 onto the plane containing the flow bed 21 lies concentrically with respect to the first feed line. The second distribution trough 27 is analogous. The two supply channels 22 of the first distributor lead from the inlet opening 31 to the first distribution trough 23 in such a manner that they form a "V" in the point of which is the inlet opening 31. Similarly, the supply channels 26 of the second distributor lead from the inlet opening 32 to the second distribution trough 27, but three supply channels are provided in the second distributor, the third extending through the middle between the two that are arranged in a V-shape.

The flow cell according to the invention can be produced, for example, from plastics, such as plexiglass, or metallic materials. However, other materials, such as glass, ceramics or semi-conductor materials are also suitable. Suitable production processes

are, depending on the material, for example machining techniques; especially precision engineering, micro machining processes, such as those used in microelectronics for structuring semi-conductor materials, and the lithographic-galvanic LIGA process.

There now follows a description of the operation and mode of functioning of the flow cell according to the invention with reference to the first embodiment. The first substance is fed in through the inlet opening 31 and the second substance is fed in through the inlet opening 32. The first substance passes through the two supply channels 22 into the distribution trough 23 where it is divided amongst the various distribution channels 24. The first substance flows through those distribution channels 24 and thus passes through the outlets 241 in the form of a plurality of physically separate thin streams and into the planar flow bed 21. In an analogous manner, and at the same time, the second substance flows through the supply channels 26 into the distribution trough 27 where it is divided amongst the distribution channels 28 and thus into physically separate thin streams. Those thin streams pass through the distribution channels 28 and their outlets 281 into the radial channels 211 of the flow bed 21. Each of the thin streams containing the second substance flows through one of the radial channels 211 and thus passes in the region of the first feed line between two adjacent thin streams containing the first substance. In that manner there is produced in the flow bed 21 a thin stream pattern in which the thin streams lie side-by-side in one plane; of every two adjacent thin streams one contains the first substance and the other contains the second substance. The effective contact surface between the two substances is increased considerably as a result. In addition, the diffusion paths between the two substances that have to be travelled for the passive mixing are markedly reduced in length. As a result, rapid and efficient mixing of the substances under laminar flow conditions takes place. In addition, the narrowing flow bed 21 "focuses" the thin streams in the direction of flow, which means that the thin streams are forced ever closer together, which further reduces the length of the diffusion paths. The flow bed 21 can narrow, for example, to capillary dimensions. The flow channel 29 then preferably has a width of from 10 μm to 1000 μm , especially of less than 600 μm , and a depth of from 10 μm to 1000 μm , especially of less than 200 μm .

In the flow cell according to the invention, rotation of the thin streams relative to one another in space or deflection or turning of the thin streams out of the plane of the flow bed 21 is not required for rapid passive mixing in the flow bed 21. For that reason the flow bed 21 is also free of the structural deflecting elements provided, for example, in known passive mixers. That brings with it considerable structural simplification and also a saving on space. As a result, the flow cell according to the invention is also simple to manufacture and suitable for economic mass production. In particular, the flow cell according to the invention can be miniaturised without difficulty and is thus also suitable for the passive mixing of small to very small volumes of substance, for example in the micro- or nano-litre range. In addition, as a result of the overall plate-like structure of the flow cell with the substantially planar flow bed, the flow cell according to the invention is suitable especially for integration into relatively complex systems of preferably modular, especially stack-like, construction. The flow cell can, especially, be produced in the very compact form of a chip. It is thus suitable as a rapid, efficient mixing apparatus for miniaturised analysis systems, such as μ -TAS. Since the flow cell according to the invention is very flexible in terms of its external geometric form, it is compatible with numerous components of relatively complex flow systems.

Especially in view of its use in miniaturisable systems, it is advantageous that the dead volumes in the flow cell according to the invention are kept to a minimum as a result of its design. Dead volumes can occur especially in corners when substance material or air bubbles that have found their way in collect in the corners and become lodged there. Such dead volumes also have an adverse effect on the mixing time required because they extend the length of the process of filling and/or emptying the flow cell. In order to reduce the dead volumes in the flow cell according to the invention, it is especially advantageous if the individual distribution channels 24, 28, as shown in Fig. 1, open into the flow bed 21 and its radial channels 211, respectively, at an oblique angle.

The preferred arcuate form of the distribution troughs 23 and 27 and of the two feed lines with the outlets 241 and 281 in the first embodiment of the flow cell according to the invention offers the advantage that the geometric path lengths of the individual thin

streams in the flow cell are substantially equal. The contribution of the flow cell to the axial dispersion of a substance zone is therefore very small. There is to be understood by "axial dispersion" the widening of a substance zone in the direction of flow.

A preferred variant of the flow cell according to the invention is as follows: in each distributor the number of supply channels is equal to the number of distribution channels. Such a design of the supply channels which has been specially adapted for the first embodiment is shown in Fig. 3. Fig. 3 is a plan view of the main body 2 of such a variant for the first embodiment. The plan view is from the base plate 3 (Fig. 2) which is not itself shown in Fig. 3. The distributor for the first substance comprises in this case a plurality of supply channels 22a which extend in the manner of a fan from the inlet opening 31 for the first substance to a distribution trough 23a for the first substance. The number of supply channels 22a corresponds to the number of distribution channels 24 for the first substance. Analogously, the distributor for the second substance has a plurality of supply channels 26a which extend in the manner of a fan from the inlet opening 32 for the second substance to a distribution trough 27a. The number of supply channels 26a of the second distributor corresponds to the number of distribution channels 28. That variant has the advantage that the individual substances are divided very uniformly amongst the associated distribution channels 24 and 28, respectively. In addition, each substance passes substantially simultaneously into all the distribution channels 24 or 28 provided for it. That measure results in a further reduction in the contribution of the flow cell to the axial dispersion of a substance zone.

A second embodiment of the flow cell according to the invention comprises, in the same way as the first, in a stack-like arrangement, the main body 2, the cover plate 4 and the base plate 3. The differences with respect to the first embodiment involve the form of the flow bed and of the distributors. Fig. 4 is a plan view of the main body 2 of the second embodiment. As in Fig. 1, the plan view in Fig. 4 is also from the cover plate 4, which is not itself shown in Fig. 4. In addition, for reasons of clarity, the components shown by a dotted line in Fig. 1 are not shown in Fig. 4. The second embodiment contains a substantially planar flow bed 21b which is in the shape of a circle which is joined at its periphery by radial channels 211b. Each of the distributors

for the substances comprises a distribution trough. The latter are not shown in Fig. 4. Each of the distribution troughs is in the form of a circular trough, the distribution troughs belonging to different distributors running concentrically. That means that the distribution troughs and also the associated supply channels are arranged in the same manner as described hereinbefore for the first embodiment and shown in Fig. 1 and Fig. 2, but the distribution troughs in the second embodiment have each been extended to form a full circle. Likewise analogously to the first embodiment, a plurality of distribution channels 24b and 28b extend from the first and second distribution troughs, respectively, through the main body 2 to their outlets 241b and 281b, respectively, and respectively into the flow bed 21b and the radial channels 211b of the flow bed 21b. The outlets 241b that belong to the first distributor lie on a first feed line and the outlets 281b that belong to the second distributor lie on a second feed line. The two feed lines are each in the form of a circle and run concentrically and thus have a common geometric centre which preferably coincides with the centre of the circular flow bed 21b. The periphery of the circular flow bed 21b lies on the feed line having the smallest radius, in this case the first feed line. On that feed line the outlets 241b are arranged in such a manner that there exists between adjacent outlets 241b in each case a space of at least the length of the diameter of a distribution channel 24b. In those spaces there begin the radial channels 211b which lead to the outlets 281b of the distribution channels 28b on the second feed line. As regards the function and the mode of operation, the same explanations as given hereinbefore for the first embodiment apply also to the second embodiment.

Of course, the variants and advantageous forms described with reference to the first embodiment can be used also for the second embodiment; in particular, for example, the variant in which the number of supply channels to the distribution trough in each of the distributors is the same as the number of distribution channels 24b or 28b is a preferred variant of the second embodiment also.

It goes without saying that the number of distribution channels 24, 28; 24b, 28b shown in Fig. 1, Fig. 2 and Fig. 4 is given by way of example. The number of distribution channels for a substance determines the number of thin streams into which the substance is divided and thus influences substantially the effective contact surface

between the different substances to be mixed. For practical reasons, the provision per distributor of up to one hundred and especially fewer than thirty distribution channels is preferred. Those distribution channels are preferably in the form of drilled holes that open at an oblique angle into the flow bed 21; 21b and that have a diameter in the range of from 10 μm to 1000 μm . With a view to the miniaturisation of the flow cell according to the invention, diameters of less than 600 μm are especially preferred. For the same reason, depths of from 10 μm to 1000 μm , especially of less than 200 μm , are preferred for the flow bed 21; 21b.

The following is a list, which is not exhaustive, of further variants and possible forms of the flow cell according to the invention.

The outlet opening 33 for the mixed substances can, for example, also be provided in the cover plate 4.

For the planar flow bed 21; 21b a large number of other geometric forms, such as generally curved outlines, are possible without departing from the scope of the invention.

It is also possible to arrange the supply channels 22, 26; 22a, 26a and the distribution troughs 23, 27; 23a, 27a in the form of cut-out portions in the same boundary surface of the main body 2 that also contains the cut-out portion for the flow bed 21; 21b. The inlet openings can then be positioned in the end face of the main body 2 or in the cover plate 4. In such a design the base plate 3 can be omitted.

A plurality of flow cells according to the invention can be arranged one after the other in the form of a cascade or one above the other in the form of a stack.

As already mentioned, the flow cell according to the invention can also be designed for the passive mixing of more than two substances. It then has an inlet opening and a distributor for each substance.

What is claimed is:

1. A flow cell for the passive mixing of at least two flowable substances, having an inlet opening (31, 32) for each substance, a common outlet opening (33) for the substances and a flow bed (21; 21b) for mixing the substances, which flow cell has a substantially plate-like structure, the flow bed (21; 21b) being substantially planar, and in which flow cell there is provided for each substance a distributor that is arranged between the inlet opening (31, 32) for the substance in question and the flow bed (21; 21b) and that divides the substance into a plurality of physically separate thin streams, and wherein the distributors supply the thin streams to the flow bed (21; 21b) in interspersed relationship so that, in the flow bed, adjacent thin streams that are in contact with one another contain different substances.

2. A flow cell according to claim 1, wherein each distributor comprises at least one supply channel (22, 26; 22a, 26a), a distribution trough (23, 27; 23a, 27a) and at least two distribution channels (24, 28; 24b, 28b), the supply channel (22, 26; 22a, 26a) extending from the associated inlet opening (31, 32) for the substance to the associated distribution trough (23, 27; 23a, 27a) and, in addition, the distribution channels (24, 28; 24b, 28b) each opening at one end into the distribution trough (23, 27; 23a, 27a) and at the other end into the flow bed (21; 21b), with the result that the substances are able to pass from the corresponding inlet opening (31, 32) through the supply channels (22, 26; 22a, 26a), the corresponding distribution trough (23, 27; 23a, 27a) and the distribution channels (24, 28; 24b, 28b) into the flow bed (21; 21b).

3. A flow cell according to claim 2, wherein the flow bed (21; 21b) narrows as the distance from the outlets (241, 281; 241b, 281b) of the distribution channels (24, 28; 24b, 28b) into the flow bed (21; 21b) increases, until it enters a flow channel (29) leading to the outlet opening (33).

4. A flow cell according to any one of the preceding claims, which comprises, in a stack-like arrangement, a cover plate (4), a main body (2) and a base plate (3) containing the inlet openings (31, 32) and the outlet opening (33), the main body (2) being arranged between the cover plate (4) and the base plate (3) and having on its

boundary surface facing the cover plate (4) a cut-out portion that forms the flow bed (21; 21b), the main body (2) also having on its boundary surface facing the base plate (3) further cut-out portions that form the supply channels (22, 26; 22a, 26a) and the distribution troughs (23, 27; 23a, 27a), it being possible furthermore for the cover plate (4) to be connected to the main body (2) in such a manner that it covers the flow bed (21; 21b), and it being possible for the base plate (3) to be connected to the main body (2) in such a manner that it covers the supply channels (22, 26; 22a, 26a) and the distribution troughs (23, 27; 23a, 27a).

5. A flow cell according to any one of claims 2 to 4, wherein each of the distribution troughs (23, 27; 23a, 27a) of the distributors is in the form of an arcuate trough, the various distribution troughs (23, 27; 23a, 27a) running concentrically, and wherein the outlets (241, 281) of the distribution channels (24, 28) belonging to a distributor into the flow bed (21) lie in each case on a feed line that is in the shape of the arc of a circle, and wherein furthermore the feed lines belonging to different distributors run concentrically with the result that they have a common geometric centre which lies in the region in which the flow bed (21) enters the flow channel (29).

6. A flow cell according to claim 5, wherein the flow bed (21) widens from the point at which it enters the flow channel (29) initially in the form of the sector of a circle the centre of which coincides substantially with the common geometric centre of the feed lines, and the periphery of which includes the feed line having the smallest radius, and wherein the flow bed (21) extends from that feed line, in the form of radial channels (211) arranged between the outlets (241) lying on that feed line having the smallest radius, to the further outwardly lying outlets (281) of the distribution channels (28).

7. A flow cell according to any one of claims 2 to 4, wherein each of the distribution troughs of the distributors is in the form of a circular trough, the various distribution troughs running concentrically, and wherein the outlets (241b, 281b) of the distribution channels (24b, 28b) belonging to a distributor into the flow bed (21b) lie in each case on a circular feed line, and wherein furthermore the feed lines belonging to different distributors run concentrically with the result that they have a common geometric centre.

8. A flow cell according to claim 7, wherein the flow bed (21b) is in the form of a circle with radial channels (211b) joining it at its periphery, the centre of the circle coinciding substantially with the common geometric centre of the feed lines, the periphery of the circle furthermore lying on the feed line having the smallest radius, and the flow bed (21b) extending from that feed line, in the form of the radial channels (211b) that are arranged between the outlets (241b) lying on that feed line having the smallest radius, to the further outwardly lying outlets (281b) of the distribution channels (28b).

9. A flow cell according to any one of claims 2 to 8, wherein the number of supply channels (22a, 26a) to the distribution troughs (23a, 27a) is equal to the number of distribution channels (24, 28) and wherein there are provided per distributor up to one hundred, especially fewer than thirty, distribution channels (24, 28).

10. A flow cell according to any one of claims 2 to 9, wherein the distribution channels (24, 28; 24b, 28b) are in the form of drilled holes that open into the flow bed at an oblique angle, and that have a diameter of from 10 μm to 1000 μm , especially of less than 600 μm .

11. A flow cell according to any one of the preceding claims, wherein the flow bed (21; 21b) has a depth of from 10 μm to 1000 μm , especially of less than 200 μm .

12. A flow cell according to any one of claims 3 to 11, wherein the flow channel (29) has a width of from 10 μm to 1000 μm , especially of less than 600 μm .

13. A flow cell according to any one of claims 3 to 12, wherein the flow channel (29) has a depth of from 10 μm to 1000 μm , especially of less than 200 μm .

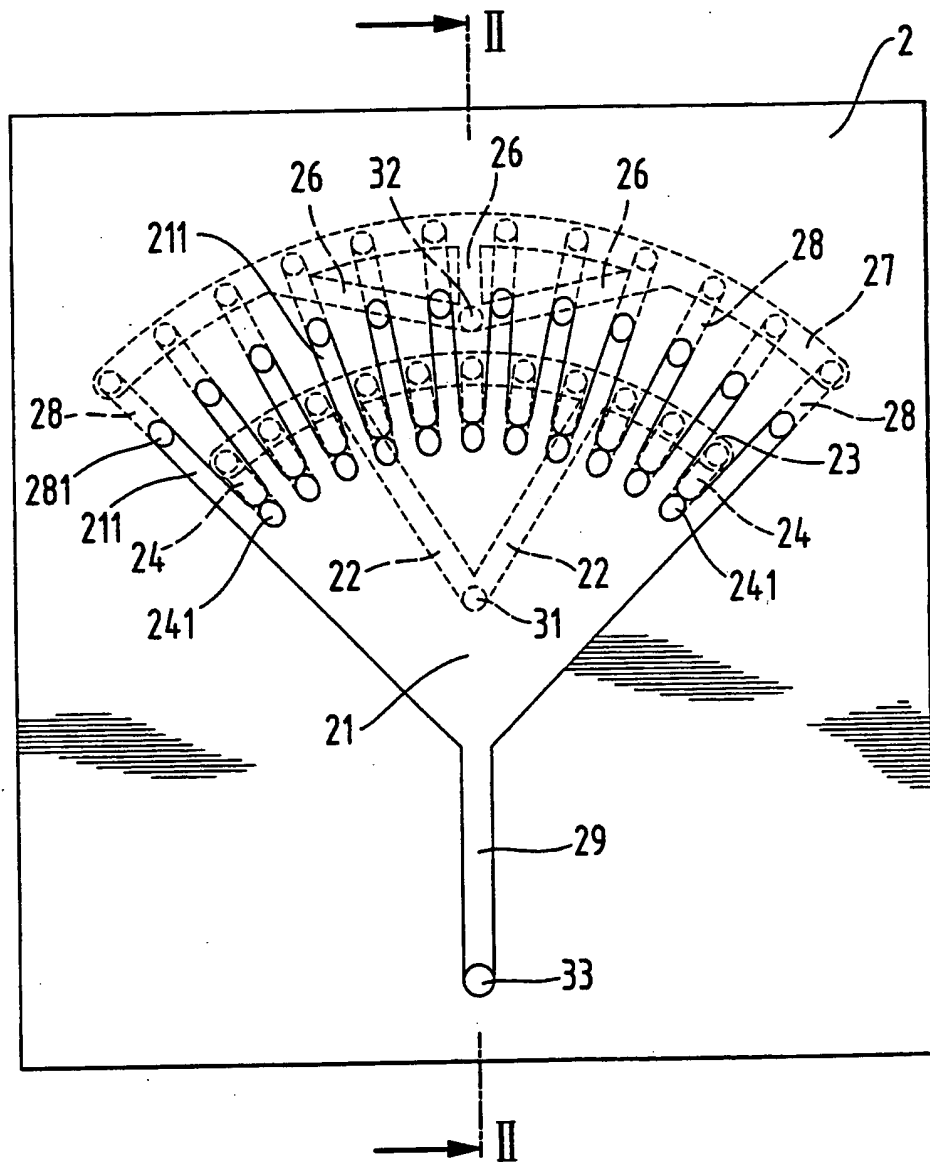
Fig. 1

Fig. 2

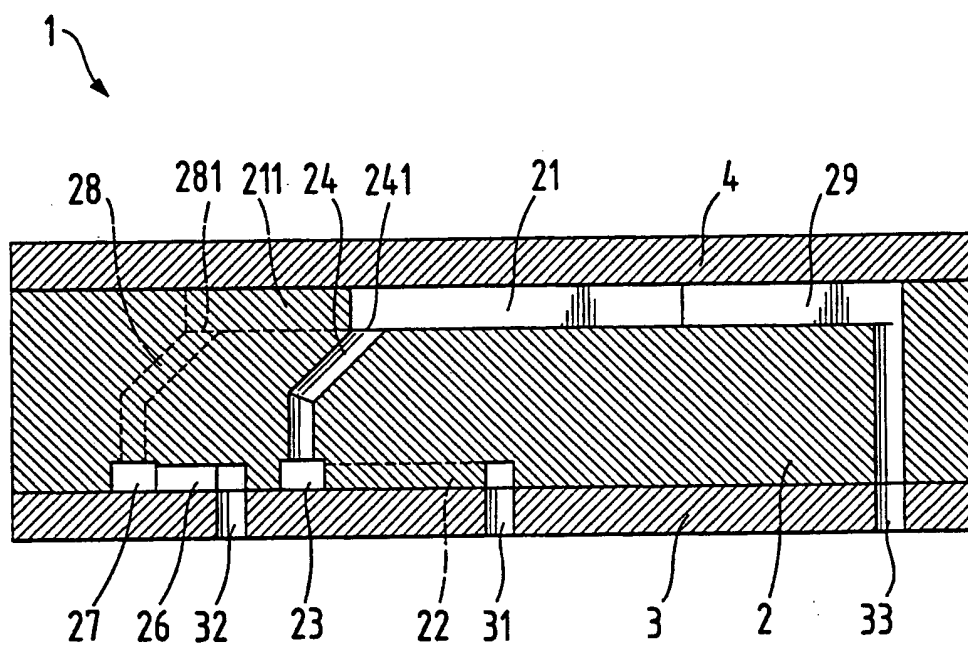


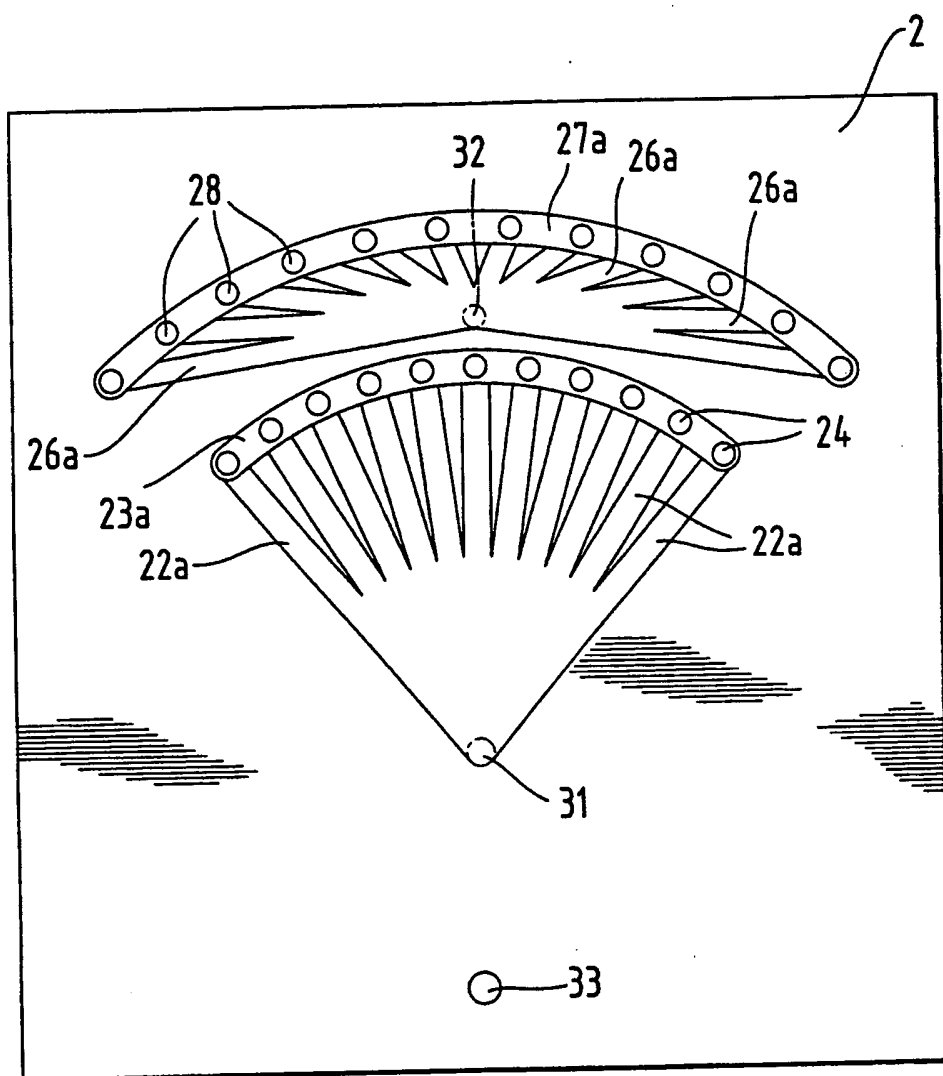
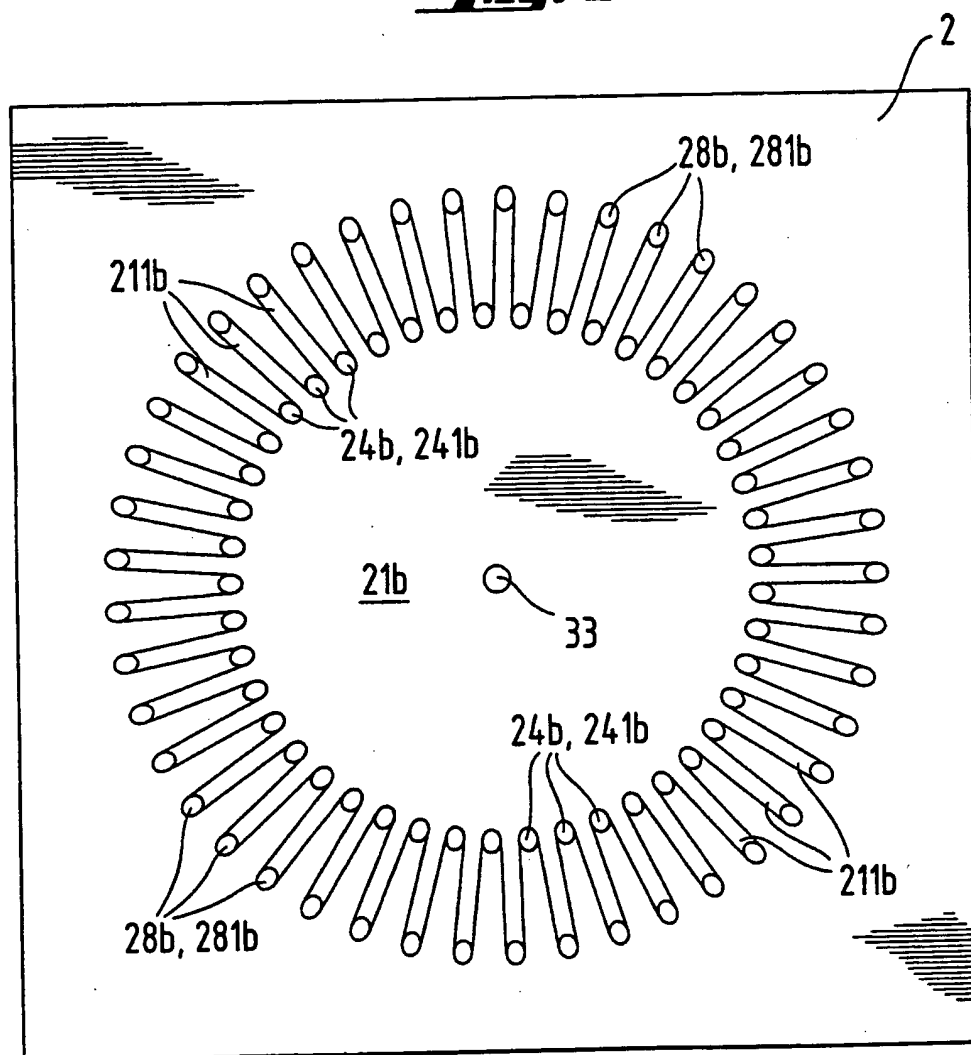
Fig. 3

Fig. 4



INTERNATIONAL SEARCH REPORT

In. ional Application No
PCT/EP 96/02425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01F5/06 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01F B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,1 254 150 (SMART & BROWN ENGINEERS LTD) 17 November 1971 see the whole document	1-7
A	GB,A,1 333 531 (DOW CORNING) 10 October 1973 see the whole document	1-4
A	WO,A,94 21372 (DU PONT) 29 September 1994 see page 20, line 7 - page 21, line 34 see page 26, line 26 - page 27, line 29; figures 4-8	1
A	US,A,3 382 534 (VEAZEY THOMAS M) 14 May 1968 see claims; figures	1
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 October 1996

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Voutsadopoulos, K

INTERNATIONAL SEARCH REPORT

In: ional Application No
PCT/EP 96/02425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO,A,93 22053 (UNIV PENNSYLVANIA) 11 November 1993 see page 5, line 1 - line 32; figures -----</p>	10-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 96/02425

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1254150	17-11-71	NONE	
GB-A-1333531	10-10-73	BE-A- 777862 DE-A- 2201016 FR-A- 2127002	10-07-72 23-11-72 13-10-72
WO-A-9421372	29-09-94	US-A- 5534328 AU-A- 6409794 BR-A- 9405989 EP-A- 0688242 JP-T- 8508197	09-07-96 11-10-94 26-12-95 27-12-95 03-09-96
US-A-3382534	14-05-68	NONE	
WO-A-9322053	11-11-93	US-A- 5304487 US-A- 5296375 AT-T- 140025 AT-T- 140880 AU-A- 4222393 AU-A- 4222593 AU-A- 4222693 AU-A- 4222793 AU-A- 4223593 CA-A- 2134474 CA-A- 2134475 CA-A- 2134476 CA-A- 2134478 DE-D- 69303483 DE-D- 69303898 EP-A- 0637996 EP-A- 0637997 EP-A- 0639223 EP-A- 0637998 EP-A- 0637999 JP-T- 7506430 JP-T- 7506431 JP-T- 7506256 JP-T- 7506257 JP-T- 7506258 WO-A- 9322054	19-04-94 22-03-94 15-07-96 15-08-96 29-11-93 29-11-93 29-11-93 29-11-93 29-11-93 11-11-93 11-11-93 11-11-93 11-11-93 08-08-96 05-09-96 15-02-95 15-02-95 22-02-95 15-02-95 15-02-95 13-07-95 13-07-95 13-07-95 13-07-95 13-07-95 11-11-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ional Application No

PCT/EP 96/02425

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9322053		WO-A- 9322421	11-11-93
		WO-A- 9322055	11-11-93
		WO-A- 9322058	11-11-93
		US-A- 5427946	27-06-95
		US-A- 5498392	12-03-96
		US-A- 5486335	23-01-96
